510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:
k123726

B. Purpose for Submission:
Addition of urine sample type to the already cleared device (k100853)

C. Measurand:
Sodium, Potassium, and Chloride

D. Type of Test:
Quantitative, indirect potentiometric measurement with ion-selective electrodes

E. Applicant:
Roche Diagnostics

F. Proprietary and Established Names:
cobas 8000 ISE Indirect Na, K, Cl for Gen. 2.

G. Regulatory Information:

1. Regulation section:
   21CFR 862.1665: Ion Specific Electrode, Sodium
   21CFR 862.1600: Ion Specific Electrode, Potassium
   21CFR 862.1170: Ion Specific Electrode, Chloride

2. Classification:
   Class II

3. Product code:
   JGS
   CEM
   CGZ

4. Panel:
   75 (Clinical Chemistry)

H. Intended Use:

1. Intended use(s):
   See Indication(s) for use below.

2. Indication(s) for use:
   The cobas 8000 ISE module is a fully automated ion-specific analyzer intended for the in vitro potentiometric determination of chloride, potassium, and sodium in serum, plasma, and urine using ion-selective electrodes. Measurements obtained by this device are used in the diagnosis and treatment of diseases or conditions involving electrolyte imbalance.

3. Special conditions for use statement(s):
   For *in vitro* diagnostic use only.
   For prescription use.

4. Special instrument requirements:
   cobas 8000 ISE Modular Analyzer

I. Device Description:

The cobas 8000 Modular Analyzer Series is a fully automated system for clinical chemistry analysis intended for the in vitro quantitative/qualitative determination of analytes in body fluids. It is optimized for high throughput workloads using a combination of ion selective electrodes (cobas 8000 1SE module) and photometric analysis modules (cobas c 701 and c 502 modules). The cobas 8000 ISE module and the ISE Gen 2 reagents were previously cleared for serum and plasma sample types under k100853. The ISE module includes a sodium electrode, a chloride electrode, a potassium electrode, a reference electrode, an ISE diluent, an ISE internal standard, an ISE reference electrolyte, an ISE calibrator and an ISE Compensator (calibrator). The ISE standard calibrators (S1, S2, and S3) were cleared under k053165 and ISE Compensator cleared under k052193.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   COBAS INTEGRA ISE System

2. Predicate 510(k) number(s):
   k963627

3. Comparison with predicate:

Similarities and Differences		
Item	**Predicate device COBAS INTEGRA ISE k963627**	**Candidate device cobas 8000 ISE Module**
Intended Use	The COBAS INTEGRA ISE module applications are intended	Same (only for sodium, potassium and chloride, no

	for use for the quantitative determination of sodium, potassium, chloride, and lithium in serum, plasma or urine using ion-selective electrodes.	lithium)
Specimen Type	Serum, Plasma, Urine	Same
Measurement Principle	ISE Potentiometry	Same
Reagent container	Plastic bottles closed via screw caps	Same
Onboard storage temperature	Room Temperature	Same
ISE Module	Integrated into Integra analyzer	Separate ISE module connected to Core cobas 8000 module
Ion Selective Electrodes (ISEs)	Potentiometric chloride, potassium, sodium and reference electrodes	Same
Sample Dilution	1:6	1:46
Throughput	Max 600 tests/hour	Max 1800 tests/hour
Detection Limits - Chloride	Not Determined	LOB = 10 mmol/L LOD = 10 mmol/L LOQ = 60 mmol/L
Reportable Range - Chloride	20-350 mmol/L	60-350 mmol/L
Detection Limits - Potassium	Not Determined	LOB = 1 mmol/L LOD = 1 mmol/L LOQ = 3 mmol/L
Reportable Range - Potassium	1-150 mmol/L	3-100 mmol/L
Detection Limits - Sodium	Not Determined	LOB = 10 mmol/L LOD = 10 mmol/L LOQ = 60 mmol/L
Reportable Range - Sodium	20-350 mmol/L	60-350 mmol/L

K. Standard/Guidance Document Referenced (if applicable):

- CLSI EP5-A2: Evaluation of Precision Performance of Clinical Chemistry

Devices

- CLSI EP6-A: Evaluation of Linearity of Quantitative Analytical Methods
- CLSI EP17-A: Protocols for Determination of Limits of Detection
- CLSI EP17-A: Protocols for Determination of Limits of Detection

L. Test Principle:

Sodium, Potassium and Chloride are measured using ion-selective electrodes utilizing an indirect (diluted) method where urine samples are automatically diluted at 1:46 ratio using ISE diluent. Each of the electrodes (Sodium, Potassium and Chloride) has membrane with an open liquid junction that is ion-selective. The reference electrode uses the same design of the ion-electrodes and it is exclusively used as a reference for every measurement. The difference of all voltages between the reference electrode and any ion-selective electrode is a measure for the concentration of individual ions. For every test, the voltages of both ISE internal standard and diluted sample solution are measured for each type of ions (Sodium, Potassium and Chloride). The measurement of all electrodes is performed in parallel. The resulting voltages are converted into operator readable results.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:
   Precision studies were performed using human urine samples and control material. Within-run precision was determined using 21 replicates for each sample type (3 urine samples and 2 controls) by one operator on one instrument. Total precision was determined using 3 samples (Low, Medium and High) over 21 days in 2 runs with one operator on one instrument. The following results were obtained:

   Sodium

Sodium	Within-run precision			Total precision		
	Mean mmol/L	SD mmol/L	CV %	Mean mmol/L	SD mmol/L	CV %
Urine low	66.4	0.4	0.6	68.6	1.1	1.6
Urine medium	178.9	0.9	0.5	180.3	1.0	0.6
Urine high	321.7	0.7	02	318.0	2.1	0.7
Liquichek 1	81.1	0.3	0.4	82.7	1.2	1.4
Liquichek 2	170.6	0.5	0.3	171.3	1.0	0.6

Potassium

Potassium	Within-run precision			Total precision		
	Mean mmol/L	SD mmol/L	CV %	Mean mmol/L	SD mmol/L	CV %
Urine low	3.65	0.00	1.2	3.75	0.06	1.7
Urine medium	51.10	0.30	0.6	49.48	0.65	1.3
Urine high	83.78	0.66	0.8	80.60	1.32	1.6
Liquichek 1	32.19	0.19	0.6	31.32	0.37	1.2
Liquichek 2	69.47	0.39	0.6	67.49	1.17	1.7

Chloride

Chloride	Within-run precision			Total precision		
	Mean mmol/L	SD mmol/L	CV %	Mean mmol/L	SD mmol/L	CV %
Urine low	63.6	0.5	0.7	64.7	1.1	1.7
Urine medium	180.8	0.9	0.5	179.7	12	0.7
Urine high	341.7	1.1	0.3	336.5	3.5	1.0
Liquichek 1	92.3	0.4	0.5	92.6	1.1	1.2
Liquichek 2	189.6	0.6	0.3	187.9	1.6	0.9

b. Linearity/assay reportable range:
Linearity studies were performed according to CLSI EP6-A. Dilution series of 11 concentrations were prepared using low and high human urine sample pools for each of the analytes and tested in triplicates. Linear regression summary results of the study are presented in the table below:

Analyte	Slope	Intercept	r2	Range Tested
Sodium	0.9914	3.1424	0.999957	54.6 – 368.8
Potassium	1.0389	0.1518	0.999597	2.9 – 101.7
Chloride	0.9425	2.7004	0.999499	48 – 384.5

The results of the study support the sponsor's claims that the urine Sodium is linear from 60 - 350 mmol/L, urine Potassium is linear from 3-100 mmol/L, and urine Chloride is linear form 60-350 mmol/L.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Aqueous ISE standard calibrators (S1, S2, and S3) were previously cleared under k053165 and ISE Compensator (calibrator) under k052193. The ISE Compensator is traceable to Flame Photometry (Sodium, Potassium) and Coulometry (Chloride).

d. *Detection limit:*
Studies were carried out in accordance with CLSI Guidance Document EP17-A for Sodium, Potassium and Chloride analytes. For determination of LoB one analyte free sample was measured in 5 replicates, 6 runs, 3 days, on 2 cobas 8000 ISE analyzers. Total of 60 measurements were obtained per analyzer. For determination of LoD, five samples (one replicate) with low-analyte concentration were measured in 6 runs for 3 days on 2 cobas 8000 ISE analyzer modules. In total 60 measurements were obtained per analyzer. For LoQ studies a low level sample set was prepared by diluting 3 human urine samples with an analyte free diluent (ISE Diluent). The low level sample set was tested in single replicate for 3 days in 2 runs per day on two cobas 8000 ISE analyzers. LoQ is defined as the concentration where total error is less than 20%. Results from the detection limit studies are summarized in the table below:

	LoB (mmol/L)	LoD (mmol/L)	LOQ (mmol/L)	Claimed measuring range (mmol/L)
Sodium	10	10	60	60-350
Potassium	1	1	3	3-100
Chloride	10	10	60	60-350

e. *Analytical specificity:*
Urine interference studies were performed in according to CLSI EP7-A2 for sodium, potassium, and chloride analytes using 2 levels of analytes (normal and abnormal). The effect of pH (3.8 – 8.2), total protein (14 – 280 mg/L), and hemoglobin (0 – 1,000 mg/dL) on analyte recovery was evaluated in these studies. Different concentrations of potential interference substances were spiked into pooled urine samples. The sponsor's definitions of non-significant interference is <10% difference between the spiked and unspiked samples. There was no significant interference for sodium, potassium, and chloride

when these analytes and interferents were tested in the concentration ranges indicated below:

Drug interferents:

Acetaminophen (paracetamol)	3000 mg/L
Ascorbic acid	4000 mg/L
Ca-Dobesilate	1000 mg/L
Gentamycin sulfate	400 mg/L
Ibuprofen	4000 mg/L
L-Dopa	1000 mg/L
Methyldopa	2000 mg/L
Na-Cefoxitin	12000 mg/L
N-Acetylcysteine	10 mg/L
Ofloxacine	900 mg/L
Phenazopyridine	300 mg/L
Salicyluric acid	6000 mg/L
Tetracycline (Doxycycline)	300 mg/L

Hemolysis:

Sodium and Chloride

Hemoglobin in urine samples does not interfere in the tested concentration range up to 1000 mg/dL (621 umol/L) hemoglobin (approximate H index 1000).

Potassium

Hemoglobin levels higher than 400 mg/dL in normal human urine samples increase the apparent potassium concentrations significantly.
Hemoglobin in pathological urine samples does not interfere in the tested concentration range up to 1000 mg/dl (621 umol/L).
Avoid hemolyzed specimens.

Icterus:

Bilirubin (conjugated) in urine samples does not interfere in the tested concentration range up to 60 mg/dl (1026 umol/L) bilirubin (approximate I index 60).

Sample	pH	Sodium		Potassium		Chloride	
		Result (mmol/L)	% of Reference	Result (mmol/L)	% of Reference	Result (mmol/L)	% of Reference
Reference	6	74.4	-	27.32	-	70.0	-
Acidic	3.8	74.2	99.7	26.77	97.99	72.6	103.7
Alkaline	8.2	74.8	100.5	26.95	98.65	67.3	96.1

f. Assay cut-off:

Not applicable

2. Comparison studies:

   a. *Method comparison with predicate device:*
   Method comparison studies were conducted for sodium, potassium and chloride on the candidate device (cobas 8000 ISE module) (y) and the results were compared to those determined with the predicate device analyzer (x). The lowest concentration and the highest concentration are diluted and spiked in order to cover hard-to-find sample range for each analyte. Results from the method comparison studies are summarized in tables below:

   Sodium

Instruments	No. Samples	Range Tested (mmol/L)	Passing Bablok	R
x:cobas INTEGRA ISE y:cobas 8000 ISE	100	62.2 – 340	y = 1.041x – 4.477	1.000

   Potassium

Instruments	No. Samples	Range Tested (mmol/L)	Passing Bablok	R
x:cobas INTEGRA ISE y:cobas 8000 ISE	100	3.4 – 100	y = 0.937x + 0.429	1.000

   Chloride

Instruments	No. Samples	Range Tested (mmol/L)	Passing Bablok	R
x:cobas INTEGRA ISE y:cobas 8000 ISE	59	61.1 – 344.3	y = 0.971x – 2.787	0.999

   b. *Matrix comparison:*
   Not applicable

3. Clinical studies:

   a. *Clinical Sensitivity:*
   Not applicable

   b. *Clinical specificity:*
   Not applicable

   c. *Other clinical supportive data (when a. and b. are not applicable):*
   Not applicable

4. Clinical cut-off**:**
   Not Applicable

5. Expected values[1]/Reference range:
   The expected values for adult based on 24 hours urine out-put are cited from the literature:

   Na+ 40-220 mmol/24 h
   K+ 25-125 mmol/24 h
   Cl- 110-250 mmol/24 h

   References:
   1. Tietz Fundamentals of Clinical Chemistry, Fifth Edition, Edited by Carl A. Burtis and Edward R. Ashwood, W.B. Saunders Company, 2001: 970, 1004, 1009 (ISBN 0-7216-8634-6).

N. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.